Procerus muscle

Make a single injection into the procerus muscle in the mid-line.

Description of Clinical Data Sources:

The primary data sources utilized by this reviewer in conducting this review are the studies conducted under Allergan's IND 8142. There was also a thorough review of the Medical Officer Review by Marc Walton, M.D., Ph.D., OTRR/DCTDA of the Complete Response Submission of November 19, 1999 and the Second CR Letter Response Submission of December 15, 2000 for PLA ——— BOTOX® for treatment of cervical dystonia.

There have been communications with the staff of the FDA Adverse Event Reporting System (AERS), which receives spontaneous reports of suspected side effects associated with licensed products, regarding the product BOTOX®. This is a passive reporting system and most of the reports have involved its licensed indications. Also, these data are often incomplete and subject to underreporting and other limitations.

The FDA Adverse Event Reporting System has cosmetic use of BOTOX® accounting for 106 of 251 (42%) adverse reports for BOTOX® between 11/1997 and 1/2001. The cosmetic use of BOTOX® does involve more reports of certain adverse events, compared to other therapeutic uses. These events are ptosis (28% vs. 10%), headache (16% vs. 3%), injection site reactions (15% vs. 3%), ecchymosis (7% vs. 1%), and facial edema (5% vs. 2%).

A thorough literature review was undertaken for the use of the product BOTOX® in the treatment of glabellar lines. These articles included, but were not limited to,

Ahn K.-Y., Botulinum toxin A for the treatment of facial hyperkinetic wrinkle lines in Koreans, *Plastic and Reconstructive Surgery,* Volume 105, Issue 2, 2000, Pages 778-784

Ahn M.S.; Catten M.; Maas C.S., Temporal brow lift using botulinum toxin A, *Plastic and Reconstructive Surgery,* Volume 105, Issue 3, 2000, Pages 1129-1135

Carruthers J.; Carruthers A., BOTOX treatment for expressive facial lines and wrinkles, *Current Opinion in Otolaryngology and Head and Neck Surgery,* Volume 8, Issue 4, 2000, Pages 357-361

Fagien S., Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: Adjunctive use in facial aesthetic surgery, *Plastic and Reconstructive Surgery*, Volume 103, Issue 2, 1999, Pages 701-713

Fagien S., Brandt F.S., Primary and adjunctive use of botulinum toxin type a (Botox) in facial aesthetic surgery: Beyond the glabella, *Clinics in Plastic Surgery,* Volume 28, Issue 1, 2001, Pages 127-148

Guerrissi J.; Sarkissian P., Local injection into mimetic muscles of botulinum toxin A for the treatment of facial lines, *Annals of Plastic Surgery,* Volume 39, Issue 5, 1997, Pages 447-453

Letessier S., Treatment of wrinkles with botulinum toxin, *Journal of Dermatological Treatment,* Volume 10, Issue 1, 1999, Pages 31-36

Paloma V.; Samper A., A complication with the aesthetic use of Botox: Herniation of the orbital fat [11], *Plastic and Reconstructive Surgery,* Volume 107, Issue 5, 15 April 2001, Page 1315

Wieder J.M.; Moy R.L., Understanding botulinum toxin: Surgical anatomy of the frown, forehead, and periocular region, *Dermatologic Surgery,* Volume 24, Issue 11, 1998, Pages 1172-1174

Summary of Clinical Studies:

Clinical Trials ——————————— were Phase 3, multicenter, double blind, randomized, parallel group studies involving the identical protocol, entitled "A Multicenter, Double Blind, Randomized, Placebo- Controlled, Parallel Study of the Safety and Efficacy Of BOTOX® (Botulinum Toxin, Type A) Purified Neurotoxin Complex in Subjects with Glabellar Lines". There were 29 centers in the U.S.A. involved and 1 center in Canada.

The objective of these studies was to evaluate the safety and efficacy of BOTOX® compared with placebo for the treatment of glabellar lines.

The study design was multicenter, double-blind, randomized, placebo-controlled, parallel-group.

There were two sets of primary hypotheses:

1. The null hypothesis was that there existed no difference in the proportion of subjects with a glabellar line severity score of 0 or 1 between the two treatment groups and the alternative hypothesis was that there was a difference.
2. The null hypothesis was that there exists no difference in the proportion of subject's with a global assessment of +2 or greater between the two treatment groups and the alternative hypothesis was that there was a difference.

The subjects were males and females age 18-75 years randomly assigned to BOTOX® treatment or placebo 3:1 ratio stratified by age group ($\leq$50 years, $\geq$ 51 years).

Inclusion Criteria:

- Glabellar lines of at least moderate severity at maximum frown
- Stable medical condition
- Willing and able to complete the entire course of the study and to comply with study instructions
- Written informed consent has been obtained.

Exclusion Criteria:

- Any medical condition that may put the subject at increased risk with exposure to BOTOX®, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function
- Concurrent use of aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function
- Evidence of recent alcohol or drub abuse
- Psychiatric problems that, in the investigator's opinion, are severe enough to interfere with study results
- Infection or skin problem at the injection site
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or inability to substantially lessen glabellar lines even by physically spreading them apart
- History of facial nerve palsy
- Females who are pregnant, nursing, or planning a pregnancy during the study period or females of childbearing potential, not using a reliable means of contraception (females of childbearing potential had to have a negative pregnancy test on Day 0 prior to injection)
- Any other planned facial cosmetic procedure during the study period
- Known allergy or sensitivity to the study medication or its components
- Concurrent participation in another clinical study or participation in the 30 days immediately prior to enrollment
- Any condition or situation that in the investigator's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

COMMENT: *FDA Review Team requested verification that the occurrence of a serious or unexpected adverse event would satisfy the criteria for discontinuation of further treatments under these protocols and discontinuation of a subject's participation in these studies but Allergan did not revise the protocols accordingly.*

The lots used in the studies were new bulk toxin [redacted] for study [redacted] and lots [redacted], for study [redacted] BOTOX® vehicle for placebo [redacted], was used for both studies.

The randomization schedule was stratified by investigator and age group, ≤50 years, ≥ 51 years. Within each age group stratum, subject numbers were assigned to treatment groups in blocks of 8:2 placebo group assignments and 6 BOTOX® group assignments. Subjects were assigned a subject number in consecutive ascending order within each age category and treatment assignment block. Treatment was distributed to investigational site in complete blocks. Someone with no other study involvement performed dilutions and prepared syringes for injection at each site. There were two evaluators at Day 0, then one for Day 7 and the other for Day 30 and one evaluator for all subsequent visits.

COMMENT: *The Review Team had requested that the block sizes be varied and not all be eight. Also, the Review Team had requested that the blocks be independent across strata.*

Study injections were not necessarily given in the same order as assignment of subject numbers. Treatment blinding was also protected by not describing the randomization block size in the study protocol. If necessary for safety and treatment of an adverse event, the investigator could unblind the subject's treatment assignment. However, during these studies, no study medication code needed to be unblinded.

At Day 0 of the study subjects received a single treatment of intramuscular injection with either placebo (BOTOX® vehicle) or BOTOX®. A vial containing either placebo or 100U of BOTOX ® was diluted with 2.5ml of sterile, non-preserved 0.9% saline, for a dilution in the active treatment groups of 40 U/mL (4 U/0.1 mL). Injection volume was 0.1ml/injection site, for a dose/injection site in the active treatment groups of 4U. Patients were injected intramuscular with a 30 gauge 1" needle on a tuberculin syringe in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 U. Subjects were observed on site 30 minutes post injection.

Subjects had a screening complete blood count, blood chemistry, serum antibodies to botulinum toxin type A, and urine pregnancy. Blood tests were repeated at Day 120.

COMMENT: *Although these were planned to be collected prior to randomization on Day 0, they were actually performed after randomization but prior to treatment.*

At post-injection Day 0, 7, 30, 60, 90, and 120 there were clinic visits and investigator questioning. The investigator asked, "How have you been feeling since the last visit?" Directed questioning and examination was done as appropriate. There was not a subject diary card. Documented adverse events on case report forms were to have date of onset, resolution date, action taken, outcome, type, severity and relationship to study drug at post injection Day 0 and 30.

If a female became pregnant, the investigator followed the progress of the pregnancy to term and documented the outcome.

Faces were photographed Day 0, 7, 30, 60, 90, 120 at 0 degrees full frontal. Each site was supplied with the same standardized equipment and processing of the film was done at a central lab. Each site received instructions and training on taking photographs. A photonumeric guide was provided to each study site to assist in grading the severity of glabellar lines.

The primary efficacy measurements were (1) the investigator's rating of glabellar line severity at maximum frown and (2) subject's global assessment of change in appearance of glabellar lines using a none, mild, moderate, severe grading scale Day 0, 7, 30, 60, 90, 120. For the investigator rating, a photoguide was provided to each study center to assist in grading the severity of glabellar lines using a 4-point grading scale of:

0=none
1=mild
2= moderate
3=severe

For the global assessment of change in appearance of glabellar lines, the subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your most recent injection?" The rating of responses were:

+4	Complete improvement (about 100%)
+3	Marked improvement (substantial improvement, about 75%)
+2	Moderate improvement (definite improvement, about 50%)
+1	Slight improvement (some improvement, about 25%)
0	Unchanged
-1	Slight worsening (about 25% worse)
-2	Moderate worsening (about 50% worse)
-3	Marked worsening (about 75%)
-4	Very marked worsening (about 100% worse or greater)

Secondary efficacy endpoint was the investigator's rating of glabellar line severity in those subjects who at baseline demonstrated a glabellar line severity score *at rest* of moderate or severe Day 0, 7, 30, 60, 90, and 120. (All subjects had to have baseline entry criteria of glabellar line severity score *with maximum frown* of moderate or severe).

COMMENTS: *The Review Team had also recommended baseline subject assessment of appearance at Day 0. Allergan did not incorporate this recommendation into the protocols.*

Criteria for effectiveness:

- A 30 percentage point difference between BOTOX® and placebo treatment groups in the incidence of subjects with an investigator's rating of glabellar line severity of none or mild at maximum frown
- A 25 percentage point difference between BOTOX® and placebo treatment groups in the incidence of subjects with a score of at least +2 (moderate improvement) in subject's global assessment of change in the appearance of glabellar lines.

Primary analyses of both primary efficacy variables were based on a binomial distribution; therefore, the sample size was determined for the smallest difference to detect with respect to the hypotheses for the two primary variables. This is a 25% point difference between the treatment groups in the proportion of subjects with a global assessment score of +2 or greater.

A total sample size of 200 subjects (for each study) was calculated based on a binomial (proportion) comparison with the following assumptions:

- Response rate in the BOTOX ® treatment group is 50% compared to 25% for the placebo treatment group.
- 3:1 ratio of BOTOX® to placebo treated subjects
- Type-I error = .05
- Type-II error = .15, or power = 85%

A planned enrollment sample size of 256 (192 BOTOX® treated and 64 placebo) would have allowed for a 20% dropout rate.

No interim analysis was planned for these studies.

Treatment of missing data:

At each visit, the mean of all non-missing data across both treatment groups would be used to replace missing values for the efficacy variables investigator's rating or glabellar line severity at maximum frown and at rest, and subject's global assessment of change in appearance of glabellar lines. This would be done using the original scores, i.e., prior to any data transformations.

In addition, for those variables assigned missing value replacements, a secondary analysis would be performed without such replacements. For the remaining variables, data would only be analyzed without replacement of missing values.

Missing values would be replaced in the analysis of the intent-to-treat dataset only. Furthermore, data would be replaced only for visits up to and including the Day 30 visit or the exit visit, whichever occurred later.

Windows for visits:

Day 7	1-15
Day 30	16-45
Day 60	46-75
Day 90	76-105
Day 120	106-high

For multiple visits within a window, the data from the visit closest to the target day would be assigned to the scheduled visit. In the event of a tie, the visit prior to the scheduled visit would be assigned.

Number and percent of responders would be calculated. A Mantel-Haenszel test stratified by age group would be performed to evaluate the equality of the proportions of responders between groups. Relative risk estimates would be calculated using the natural logarithms of the stratum relative risk ratios and precision based weights.

The Fisher's exact test would be performed to test for between-group differences for the tabulation of all adverse events regardless of treatment relatedness and severity.

Within-group analyses would be performed on vital signs using the Wilcoxon signed-rank test. Between-group analyses would be performed for exit data using the Wilcoxon rank-sum test.

Within-group analyses would be performed on laboratory parameters using the Wilcoxon signed-rank test. Between-group analyses would be performed for exit data using the Wilcoxon rank-sum test.

Data was to be summarized with descriptive statistics, frequency tables, data listings, by investigator and by demographic subgroups for age, gender and race.

Subgroup analysis would be performed for the follow groups:

- Age (≤50 years, ≥ 51)
- Race (white, non-white)
- Sex (male, female)
- Investigator (this was later dropped)

COMMENT: *FDA Review Team asked that additional subgroup analyses for safety and efficacy be included for age ≥ 65 years, history of previous BOTOX® treatment for glabellar lines, and primary efficacy analyses by baseline severity of glabellar lines at maximum frown (moderate or severe). Because there were so few values imputed, all subgroup analyses included the values imputed over the entire data set, and a secondary analysis with observed cases only was not performed by Allergan.*

Intent-to-treat analyses were the primary safety and efficacy analyses and included all randomized subjects. Subjects who met the evaluability criteria as specified in the analysis plan, and received study medication with at least one follow-up visit would be included in the per protocol analysis. Continuous variables would be summarized with descriptive statistics. Paired t-tests were to be performed for change from baseline analyses and two-sample t-tests performed for between-group comparisons. If the data were not transformable to symmetry appropriate non-parametric methods would be used. Confidence intervals were to be 95% two-sided intervals based on the t-distribution.

COMMENT: *The Review Team informed Allergan that symmetry is not enough for the t-test to be valid. Normality and equal variances would also be required. Thus, they recommended that a nonparametric method be used regardless of how symmetric the data appeared.*

There are two co-primary efficacy endpoints at Day 30:

- The incidence of subjects with a glabellar line severity of none or mild at maximum frown
- The incidence of subjects with a score of +2 or greater in subject's global assessment of change in appearance of glabellar lines

The primary analysis is on data collected on the two efficacy variables at Day 30 post-injection. Glabellar line severity scores are dichotomized to represent responders (scores 0 and 1) and non-responders (scores of 2 and 3). Results of the primary analysis are considered statistically significant if the P-value is less than or equal to .05 for each of these variables.

Safety variables are adverse events, hematology, electrolytes, and blood chemistry, and vital signs. Allergan's modified COSTART nomenclature was used to code adverse events. For each adverse event reported, the number and percent of subjects was tabulated. Tables were generated by relationship to treatment as well as by body system.

COMMENTS: *The Review Team had also recommended that subjects be called at 48 hours post injection and that subjects be queried for certain specific adverse events that had been observed in previous off-label BOTOX® clinical trials. Allergan did not incorporate these recommendations into the protocols.*

A serious adverse event was defined as any adverse event occurring at any dose that resulted in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Others could be added based upon appropriate medical judgment.

The severity of an adverse event was graded as:

Mild: Awareness of sign or symptom, but easily tolerated

Moderate: Discomfort enough to cause interference with usual activity

Severe: Incapacitating with inability to work or do usual activity

Not applicable: In some cases, could be an "all or nothing" finding that could not be graded.

Use of concurrent medication, prescription or over-the-counter, was to be recorded on the subject's case report form along with the reason the medication was taken. Subjects would continue their standard facial skin care regimen throughout the duration of the study.

Reasons for non-compliance considered having potential to confound a subject's efficacy results included the following:

1. Facial cosmetic procedure during the study period.
2. The same evaluator at both Day 7 and Day 30 for a given subject.

Results:

Clinical Trial

There were 14 US sites involved.

There were 264 subjects enrolled into the study and 261 completed the study.

- 2 dropouts were in the BOTOX® treatment group
  - Subject 2934-J10 moved after the Day 90 visit without notification
  - Subject 2936-F59 dropped out due to illness in family at Day 28
- 1 dropout was randomized to the placebo group but never received treatment.
  - Subject 2935-G02 did not want to wait in the office 30 minutes after treatment.

There were 203 that received BOTOX® and 61 that received placebo.

There were 85 subjects (68 BOTOX® treated subjects and 17 placebo treated subjects) who had baseline scores at rest of moderate or severe.

The age range was 23-76 years with the mean being 44.6.

- 74.2% of subjects were ≤ 50 years of age
- 4.9% of subjects were ≥ 65 years of age

There were 220 females (83%) and 44 males (17%).

There were 223 Caucasians (85%).
There were 22 Hispanics (8%).
There were 8 African-Americans (3%).
There were 7 Asians (3%).
There were 4 other races (2%).

Most subjects had not had any prior treatment with BOTOX®.

- 13.8% (28/203) in the BOTOX® group had a prior history
- 11.7% (7/60) in the placebo group had a prior history

Protocol violations:

- Subject 2935-G02 enrolled, signed the consent form and randomized to placebo but then dropped out due to the requirement to wait 30 minutes post treatment
- Subject 2935-G12 had a dermapeel (assigned to BOTOX® group)
- Subject 2935-G13 had a dermapeel (assigned to BOTOX® group)
- Subject 2935-G15 had a dermapeel (assigned to BOTOX® group)
- Subject 3187-P03 had collagen injections (assigned to BOTOX® group)
- Subject 3187-P58 had collagen injections (assigned to BOTOX® group)
- Subject 3187-P59 had permanent eyebrows tattooed (assigned to placebo group)
- Subject 2046-C09 was evaluated at Days 7 and 30 by the same investigator (assigned to BOTOX® group)
- Subject 2046-C11 was evaluated at Days 7 and 30 by the same investigator (assigned to BOTOX® group)
- Subject 2046-C12 was evaluated at Days 7 and 30 by the same investigator (assigned to BOTOX® group)
- Subject 1996-R02 became pregnant (assigned to BOTOX® group). Pregnancy was terminated.

There were 8 deviations from the planned randomization:

- Subject number 2935-G59 was inadvertently skipped (assigned to BOTOX® group).
- Subject number 2046-C18 was inadvertently skipped (assigned to BOTOX® group).
- Subject number 2046-C20 was inadvertently skipped (assigned to BOTOX® group).
- Subject number 2046-C19 was inadvertently skipped (assigned to placebo group).
- Subject 2046-C15 was inadvertently randomized to the ≤ 50 years age-group stratum (assigned to BOTOX® group).
- Subject 2046-C17 was inadvertently randomized to the ≤ 50 years age-group stratum (assigned to BOTOX® group).
- Subject 1996-R09 was inadvertently randomized to the ≤ 50 years age-group stratum (assigned to BOTOX® group).

- Subject 2939-H57 was inadvertently randomized to the ≥ 51 years age-group stratum (assigned to BOTOX® group).

Subject 2935-G02-had missing birth data but was analyzed according to his randomization assignment of ≤ 50 years.

Efficacy:
The analysis for efficacy was intent-to-treat (ITT), including all randomized subjects.

The highest responder rate in the BOTOX® treated group was 83.7% at Day 30 (the efficacy endpoint day) compared to 1.6% in the placebo group for the investigator's rating of glabellar line severity at maximum frown and 90.1% versus 1.6% for the subject's global assessment of change in appearance of glabellar lines.

For the secondary efficacy endpoint, for those subjects who had a baseline glabellar line severity score at rest of moderate or severe (85 subjects), the response rate was statistically higher at all timepoints for the BOTOX® treated subjects compared to placebo.

For subgroup analyses, the response rate with BOTOX® tended to be higher for subjects ≤ 50 years old than for those ≥ 51 years old.

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT MAXIMUM FROWN (% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	82.3% 167/203	4.9% 3/61	77.4% (69.8, 84.9)	<0.001
30	83.7% 170/203	1.6% 1/61	82.1% (76.1, 88.1)	<0.001
60	74.8% 151/202	0.0% 0/60	74.8% (68.8, 80.7)	<0.001
90	50.0% 101/202	0.0% 0/60	50.0% (43.1, 56.9)	<0.001
120	26.2% 53/202	0.0% 0/60	26.2% (20.2, 32.3)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR SUBJECT'S ASSESSMENT OF APPEARANCE (% and number of subjects with at least moderate improvement)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	85.7% 174/203	4.9% 3/61	80.8% (73.5, 88.1)	<0.001
30	90.1% 183/203	1.6% 1/61	88.5% (83.3, 93.7)	<0.001

60	84.7% 171/202	1.7% 1/60	83.0% (77.1, 88.9)	<0.001
90	65.8% 133/202	1.7% 1/60	64.2% (56.9, 71.5)	<0.001
120	44.1% 89/202	0.0% 0/60	44.1% (37.2, 50.9)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT REST IN SUBJECTS WITH MODERATE OR SEVERE SCORE AT BASELINE
(% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	69.1% 47/68	29.4% 5/17	39.7% (15.4, 64.0)	0.004
30	79.4% 54/68	23.5% 4/17	55.9% (33.6, 78.2)	<0.001
60	76.5% 52/68	29.4 5/17	47.1% (23.2, 71.0)	<0.001
90	77.9% 53/68	41.2% 7/17	36.8% (11.4, 62.2)	0.005
120	67.6% 46/68	35.3% 6/17	32.4% (7.1, 57.7)	0.022

95% confidence intervals are shown in parentheses

Responder Rates of Glabellar Line Severity Age
BY AGE DISTRIBUTION

	Investigator's Assessment at Maximum Frown % rated 0 or 1 ≤ 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	84.9% 129/152	6.8% 3/44	74.5% 38/51	0% 0/17	55.6% 5/9	0% 0/4
30	87.5% 133/152	2.3% 1/44	72.5% 37/51	0% 0/17	55.6% 5/9	0% 0/4
60	77.0% 117/152	0% 0/43	68.0% 34/50	0% 0/17	33.3% 3/9	0% 0/4
90	52.6% 80/152	0% 0/43	42.0% 21/50	0% 0/17	44.4% 4/9	0% 0/4
120	28.9% 44/152	0% 0/43	18.0% 9/50	0% 0/17	11.1% 1/9	0% 0/4

Responder Rates of Glabellar Line Severity
BY AGE DISTRIBUTION

	Subject's Assessment % +2 or better ≤ 50 years		Subject's Assessment % +2 or better > 50 years		Subject's Assessment % +2 or better > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	89.5% 136/152	6.8% 3/44	74.5% 38/51	0% 0/17	66.7% 6/9	0% 0/4
30	93.4% 142/152	2.3% 1/44	80.4% 41/51	0% 0/17	66.7% 6/9	0% 0/4
60	88.8% 135/152	2.3% 1/43	72.0% 36/50	0% 0/17	55.6% 5/9	0% 0/4
90	67.8% 103/152	2.3% 1/43	60.0% 30/50	0% 0/17	66.7% 6/9	0% 0/4
120	48.0% 73/152	0% 0/43	32.0% 16/50	0% 0/17	0% 0/9	0% 0/4

The response rate with BOTOX® tended to be higher for females than for males.

Responder Rates of Glabellar Line Severity
BY SEX

	Investigator's Assessment % rated 0 or 1 At Maximum Frown MALE		Investigator's Assessment % rated 0 or 1 At Maximum Frown FEMALE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
7	63.3% 19/30	7.1% 1/14	85.5% 148/173	4.3% 2/47
30	66.7% 20/30	7.1% 1/14	86.7% 150/173	0% 0/47
60	60.0% 18/30	0% 0/13	77.3% 133/172	0% 0/47
90	33.3% 10/30	0% 0/13	52.9% 91/172	0% 0/47
120	10.0% 3/30	0% 0/13	29.1% 50/172	0% 0/47

Responder Rates of Glabellar Line Severity
BY SEX

	Subject's Assessment % +2 or better MALE		Subject's Assessment % +2 or better FEMALE	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
7	73.3% 22/30	7.1% 1/14	87.9% 152/173	4.3% 2/47
30	73.3% 22/30	7.1% 1/14	93.1% 161/173	0% 0/47
60	70.0% 21/30	0% 0/13	87.2% 150/172	2.1% 1/47
90	40.0% 12/30	0% 0/13	70.3% 121/172	2.1% 1/47
120	30.0% 9/30	0% 0/13	46.5% 80/172	0% 0/47

The response rate with BOTOX® tended to be higher for Caucasians than for non-Caucasians.

Responder Rates of Glabellar Line Severity
BY RACE

	Investigator's Assessment At Maximum Frown % rated 0 or 1 CAUCASIAN		Investigator's Assessment At Maximum Frown % rated 0 or 1 NON-CAUCASIAN	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
30	85.6% 149/174	2.0% 1/49	72.4% 21/29	0% 0/12

Responder Rates of Glabellar Line Severity
BY RACE

	Subject's Assessment % +2 or better CAUCASIAN		Subject's Assessment % +2 or better NON-CAUCASIAN	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
30	90.8% 158/174	2.0% 1/49	86.2% 25/29	0% 0/12

The response rate with BOTOX® tended to be higher for subjects who had prior BOTOX® treatment for facial lines.

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Investigator's Assessment At Maximum Frown % rated 0 or 1 YES		Investigator's Assessment At Maximum Frown % rated 0 or 1 NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	92.9% 26/28	0% 0/7	82.3% 144/175	0% 0/53

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Subject's Assessment % +2 or better YES		Subject's Assessment % +2 or better NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	89.3% 25/28	0% 0/7	90.3% 158/175	0% 0/53

The response rate with BOTOX® tended to be higher for subjects whose baseline severity score was moderate than for subjects whose baseline severity score was severe.

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE		Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
7	97.6% 81/83	7.4% 2/27	71.7% 86/120	0% 0/33
30	98.8% 82/83	0% 0/27	73.3% 88/120	0% 0/33
60	95.1% 78/82	0% 0/27	60.8% 73/120	0% 0/33
90	74.4% 61/82	0% 0/27	33.3% 40/120	0% 0/33
120	41.5% 34/82	0% 0/27	15.8% 19/120	0% 0/33

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Subject's Assessment % +2 or better MODERATE		Subject's Assessment % +2 or better SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
7	94.0% 78/83	7.4% 2/27	80.0% 96/120	0% 0/33
30	97.6% 81/83	0% 0/27	85.0% 102/120	0% 0/33
60	92.7% 76/82	0% 0/27	79.2% 95/120	3.0% 1/33
90	78.0% 64/82	0% 0/27	57.5% 69/120	3.0% 1/33
120	58.5% 48/82	0% 0/27	34.2% 41/120	3.0% 1/33

Responder Rates of Glabellar Line Severity

	Investigator's Assessment at Maximum Frown % rated 0 or 1		Subject's Assessment % +2 or better		Investigator's Assessment at Rest % rated 0 or 1	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	82.3% 167/203	4.9% 3/61	85.7% 174/203	4.9% 3/61	69.1% 47/68	29.4% 5/17
30	83.7% 170/203	1.6% 1/61	90.1% 183/203	1.6% 1/61	79.4% 54/68	23.5% 4/17
60	74.8% 151/203	0.0% 0/60	84.7% 171/202	1.7% 1/60	76.5% 52/68	29.4% 5/17
90	50.0% 101/202	0.0% 0/60	65.8% 133/202	1.7% 1/60	77.9% 53/68	41.2% 7/17
120	26.2% 53/202	0.0% 0/60	44.1% 89/202	0.0% 0/60	67.6% 46/68	35.3% 6/17

Responder Rate Difference (BOTOX®- Placebo) For Each Type of Evaluation of Glabellar Line Severity

DAY	Investigator's Assessment at Maximum Frown % rated 0 or 1	Subject's Assessment of Moderate Improvement % +2 or better	Investigator's Assessment at Rest % rated 0 or 1
7	77.4% (69.8, 84.9)	80.8% (73.5, 88.1)	39.7% (15.4, 64.0)
30	82.1% (76.1, 88.1)	88.5% (83.8, 93.7)	55.9% (33.6, 78.2)
60	74.8% (68.8, 80.7)	83.0% (77.1, 88.9)	47.1% (23.2, 71.0)
90	50.0% (43.1, 56.9)	64.2% (56.9, 71.5)	36.8% (11.4, 62.2)
120	26.2% (20.2, 32.2)	44.1% (37.2, 50.9)	32.4% (7.1, 57.7)

95% confidence intervals are shown in parentheses

Safety:
No subject died during the study.

No subject discontinued the study because of adverse events.

Severe adverse events were reported for 3.4% (7/203) of subjects in the BOTOX® treatment group and none in the placebo treatment group.

- Tooth abscess
- Vaginal bleeding secondary to elective abortion
- Thrombophlebitis
- Dyspepsia
- Cutaneous inflammation
- Ovarian disorder
- Elevated creatine phosphokinase.

Serious adverse events were experienced by 2 subjects treated with BOTOX® and no subjects treated with placebo.

- Subject female who at the Day 90 follow up reported that she had been hospitalized for thrombophlebitis approximately 3 months after BOTOX® treatment. She had been taking oral contraceptives.
- Subject female who had an abnormal Pap and pelvic sonogram before enrollment. She was diagnosed with a serous tumor of the left ovary of low malignant potential a few days before her treatment with BOTOX® and underwent surgery two months later.

Laboratory: Subject [redacted] in the BOTOX® treated group had baseline ALT and AST levels that were elevated. He was also discovered to have an initially normal creatine phosphokinase level, which became elevated one month post treatment. The ALT and AST returned to normal but the CPK remained elevated. The patient admitted to using creatine as a supplement.

Overall individual abnormalities in laboratory variables did not show any clinically meaningful differences between the treatment groups. For ALT, AST, bicarbonate, and triglycerides, more subjects shifted from normal to high than from normal to low. However, the proportions who shifted were similar between treatment groups except for triglycerides, in which 7.7% (15/194) of subjects treated with BOTOX® shifted from normal at baseline to high after treatment compared with 1.7% (1/59) of placebo subjects. On the other hand, 6.2% (12/194) of subjects treated with BOTOX® shifted from high at baseline to normal after treatment.

Adverse events were reported for 47.3% (96/203) of subjects treated with BOTOX® and 36.7% of subjects treated with placebo.

Adverse events reported for ≥ 3% of subjects treated with BOTOX®:

	BOTOX N=203	**PLACEBO** N=60
Any event	96 (47.3%)	22 (36.7%)
Headache	31 (15.3%)	9 (15.0%)
Blepharoptosis	11 (5.4%)	0 (0%)
Respiratory infection	10 (4.9%)	5 (8.3%)
Nausea	7 (3.4%)	1 (1.7%)
Flu syndrome	6 (3.0%)	1 (1.7%)
Muscle weakness	6 (3.0%)	0 (0%)

The only significant difference between the groups was the incidence of blepharoptosis with a p-value of 0.074. Ptosis was unilateral in all but one subject (2934-J01). Most cases were considered mild with an average duration of 20 days. 4 cases were considered moderate with an average duration of 40 days. All subjects were female. 9 were Caucasian and 2 non-Caucasian. 7 were ≤ 50 years of age and 4 were ≥ 51 years of age. 10 subjects had no previous history of treatment with BOTOX® and 1 subject did have a previous history.

Six study sites had reported ptosis:

- 2137 23% (3/13)
- 2940 25% (3/12)
- 0093 13% (2/15)
- 3187 9% (1/11)
- 2934 7% (1/15)

- 2941 7% (1/15)

Subgroup analyses of adverse events by age, sex, race and prior BOTOX® treatment showed no statistically significant differences between the treatment groups.

There were no statistically significant differences between the groups in changes from baseline to study exit for heart rate and blood pressure.

At the time of study exit, there were 21 adverse events (16 subjects) still ongoing. 10 have since resolved. 8 are chronic conditions. 2 have been lost to follow-up.

There were 188 subjects with sufficient volume to permit antibody analysis at both pretreatment and posttreatment timepoints.

- 156 were negative at both timepoints
- 29 subjects were inconclusive at one timepoint (2 had a prior history of BOTOX® treatment)
- 4 subjects were positive at one of the timepoints (2 were positive pretreatment but not posttreatment).

Two subjects with matched pretreated and posttreatment serum antibody samples assayed had positive posttreatment samples. One was in the BOTOX® treated group and one was in the placebo treated group.

Clinical Trial :

There were 15 US sites and 1 Canadian site involved.
There were 273 subjects enrolled into the study and 268 completed the study.
There were 202 that received BOTOX® and 71 that received placebo.
There were 125 subjects (93 BOTOX® treated subjects and 32 placebo treated subjects) who had baseline scores at rest of moderate or severe.

- The distribution was the same in the BOTOX® treated subjects (41% moderate and 59% severe) and the placebo treated subjects (41% moderate and 59% severe).

The age range was 23-78 years with the mean being 47.3.
There were 7% (19/273) of subjects who were ≥ 65 years of age.

- 14 subjects in the BOTOX® treatment
- 5 subjects in the placebo group

There were more females. No subject had received BOTOX® treatment prior.

There were 220 females (81%) and 53 males (19%).

- More of the subjects were male than female at study center 3163

There were 227 Caucasians (83%).
There were 19 Hispanics (7%).
There were 20 African-Americans (7%).

- No black males were treated with BOTOX®
- The majority of black subjects were located at study center 2425

There were 6 Asians (2%).
There was 1 other race (<1%).

A higher proportion of subjects were ≤ 50 years of age (62.3%, 170/273) than were ≥ 51 years of age (37.7%, 103/273).

- All 8 subjects at study center 3155 were younger than 50 years.
- The majority of subjects at center 3158 and 3162 were older than 51 years
- There were a lower proportion of males in the older age group for the BOTOX® treatment subjects (13.5% vs. 24.2%)
- There were more blacks in the older age-group for both treatment groups (10.8% vs. 4.7% for the BOTOX® treatment group and 13.8% vs. 4.8% for the placebo treatment group)
- There were fewer Hispanics in the older age-group for both treatment groups (1.4% vs. 10.2% for the BOTOX® treatment group and 0% vs. 11.9% for the placebo group)

The treatment groups were similar with regard to previous BOTOX® treatment

- 14.9% (30/202) of the BOTOX® treated subjects
- 14.1% (10/71) of the placebo treated subjects

Placebo subjects had been treated twice as long (27.9 months) compared to the BOTOX® treatment group (13.6 months).

5 subjects dropped out-

- Subject 2425-Z61 (BOTOX® treatment) lost to follow-up
- Subject 3161-102 (BOTOX® treatment) lost to follow-up
- Subject 2425-Z12 (placebo treatment) lost to follow-up
- Subject 3155-201 (placebo treatment) left study due to travel schedule
- Subject 3162-W57 (placebo randomized) excluded due to participation in another clinical study

There were 6 subjects with protocol deviations

- 2 subjects had concomitant facial procedures-
  - Subject 2425-Z67 (BOTOX® treatment) had autologous fat transplant to the face
  - Subject 3166-405 (placebo treatment) had excision of telangiectasia by hyfrecation.

- 4 subjects were not evaluated by different investigators at Days 7 and 30
  - Subject 3157-611 (BOTOX® treatment)
  - Subject 3157-659 (BOTOX® treatment)
  - Subject 3158-U60 (BOTOX® treatment)
  - Subject 3157-613 (placebo treatment)

2 subjects were enrolled although they exceeded the age limit of 75 years

- Subject 3158-U59 (BOTOX® treatment)
- Subject 3158-U60 (BOTOX® treatment)

4 subjects were inadvertently randomized to the wrong age group ≤ 50 years

- Subject 3157-602 (BOTOX® treatment)
- Subject 3157-603 (BOTOX® treatment)
- Subject 3160-V07 (placebo treatment)
- Subject 3159-Y03 (placebo treatment)

1 subject was inadvertently randomized to the wrong age group ≥ 51 years

- Subject 2425-Z57 (BOTOX® treatment)

Data from these subjects were analyzed in the age-group stratum corresponding to their actual ages, regardless of the age-group stratum for randomization. However, a sensitivity analysis was performed to evaluate the effect of analyzing subjects by the treatment group they would have been assigned to. The results did not differ substantially from those presented for the overall study population.

The proportion of subjects who discontinued medication used in the week prior to the injection visit was similar in both groups and 2.6% overall.

There were 216 subjects (79.7%) who received concomitant medications. A similar proportion of subjects in each treatment group received concomitant medications. A higher proportion of subjects in the BOTOX® treated group reported taking propionic acid derivatives (12.9% vs. 8.6%). A higher proportion of subjects in the placebo group reported taking estrogens (15.7% vs. 9.0%). A higher proportion of subjects in the placebo group reported taking multivitamins (15.7% vs. 5.5%).

Missing data was imputed for two of three discontinued subjects:

- Subject 2934-J10 at Day 120 (missed visit)
- Subject 2935-G02 at Days 0, 7, 30 who was randomized but not treated

Efficacy:
The analysis for efficacy was intent-to-treat (ITT), including all randomized subjects. There were 202 subjects in the BOTOX® treated group and 71 subjects in the placebo treated group.

The highest responder rate in the BOTOX® treated group was 76.7% at Day 30 (the efficacy endpoint day) compared to 4.2% in the placebo group for the investigator's rating of glabellar line severity at maximum frown and 88.6% versus 11.3% for the subject's global assessment of change in appearance of glabellar lines.

For the secondary efficacy endpoint, for those subjects who had a baseline glabellar line severity score at rest of moderate or severe (125 subjects), the response rate was statistically higher at all timepoints for the BOTOX® treated subjects compared to placebo except Day 120.

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT MAXIMUM FROWN (% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	65.3% 132/202	7.0% 5/71	58.3% (49.5, 67.2)	<0.001
30	76.7% 155/202	4.2% 3/71	72.5% (65.0, 80.0)	<0.001
60	65.7% 132/201	2/9% 2/70	62.8% (55.2, 70.5)	<0.001
90	45.3% 91/201	4.4% 3/68	40.9% (32.4, 49.3)	<0.001
120	24.4% 49/201	2.9% 2/68	21.4% (14.3, 28.6)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR SUBJECT'S ASSESSMENT OF APPEARANCE (% and number of subjects with at least moderate improvement)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	79.2% 160/202	12.7% 9/71	66.5% (57.0, 76.1)	<0.001
30	88.6% 179/202	11.3% 8/71	77.4% (68.8, 85.9)	<0.001
60	79.1% 159/201	5.7% 4/70	73.4% (65.6, 81.2)	<0.001
90	60.2% 121/201	4.4% 3/68	55.8% (47.4, 64.1)	<0.001
120	33.8% 68/201	1.5% 1/68	32.4% (25.2, 39.5)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT REST IN SUBJECTS WITH MODERATE OR SEVERE SCORE AT BASELINE (% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	67.7% 63/93	21.9% 7/32	45.9% (28.7, 63.1)	<0.001
30	69.9% 65/93	18.8% 6/32	51.1% (34.7, 67.6)	<0.001
60	69.9% 65/93	21.9% 7/32	48.0% (30.9, 65.1)	<0.001
90	65.6%	31.3%	34/3%	0.001

	61/93	10/32	(15.6, 53.1)	
120	52.7% 49/93	34.4% 11/32	18.3% (-1.0, 37.7)	0.113

95% confidence intervals are shown in parentheses

Responder Rates of Glabellar Line Severity

	Investigator's Assessment at Maximum Frown % rated 0 or 1		Subject's Assessment % +2 or better		Investigator's Assessment at Rest % rated 0 or 1	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
7	65.3% 132/202	7.0% 5/71	79.2% 160/202	12.7% 9/71	67.7% 63/93	21.9% 7/32
30	76.7% 155/202	4.2% 3/71	88.6% 179/202	11.3% 8/71	69.9% 65/93	18.8% 6/32
60	65.7% 132/201	2.9% 2/70	79.1% 159/201	5.7% 4/70	69.9% 65/93	21.9% 7/32
90	45.3% 91/201	4.4% 3/68	60.2% 121/201	4.4% 3/68	65.6% 61/93	31.3% 10/32
120	24.4% 49/201	2.9% 2/68	33.8% 68/201	1.5% 1/68	52.7% 49/93	34.4% 11/32

Responder Rate Difference (BOTOX®- Placebo) For Each Type of Evaluation of Glabellar Line Severity

DAY	Investigator's Assessment at Maximum Frown % rated 0 or 1	Subject's Assessment of Moderate Improvement % +2 or better	Investigator's Assessment at Rest % rated 0 or 1
7	58.3% (49.5, 67.2)	66.5% (57.0, 76.1)	45.9% (28.7, 63.1)
30	72.5% (65.0, 80.0)	77.4% (68.8, 85.9)	51.5% (34.7, 67.6)
60	62.8% (55.2, 70.5)	73.4% (65.6, 81.2)	48.0% (30.9, 65.1)
90	40.9% (32.4, 49.3)	55.8% (47.4, 64.1)	34.3% (15.6, 53.1)
120	21.4% (14.3, 28.6)	32.4% (25.2, 39.5)	18.3% (-1.0, 37.7)

For subgroup analyses, the response rate with BOTOX® tended to be higher for subjects ≤ 50 years old than for those ≥ 51 years old.

Responder Rates of Glabellar Line Severity Age
BY AGE DISTRIBUTION

	Investigator's Assessment at Maximum Frown % rated 0 or 1 ≤ 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	75.8% 97/128	4.8% 2/42	47.3% 35/74	10.3% 3/29	21.4% 3/14	20.0% 1/5
30	81.3% 104/129	2.4% 1/42	68.9% 51/74	6.9% 2/29	28.6% 4/14	40.0% 2/5
60	69.5% 89/128	2.4% 1/42	58.9% 43/73	3.6% 1/28	28.6% 4/14	25.0% 1/4
90	47.7% 61/128	2.5% 1/40	41.1% 30/73	7.1% 2/28	214.% 3/14	25.0% 1/4
120	28.1% 36/128	0% 0/40	17.8% 13/73	7.1% 2/28	0% 0/14	25.0% 1/4

Responder Rates of Glabellar Line Severity Age
BY AGE DISTRIBUTION

	Subject's Assessment % +2 or better ≤ 50 years		Subject's Assessment % +2 or better > 50 years		Subject's Assessment % +2 or better > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	83.6% 107/128	7.1% 3/42	71.6% 53/74	20.7% 6/29	42.9% 6/14	20.0% 1/5
30	89.8% 115/128	4.8% 2/42	86.5% 64/74	20.7% 6/29	71.4% 10/14	20.0% 1/5
60	79.7% 102/128	4.8% 2/42	78.1% 57/73	7.1% 2/28	71.4% 10/14	0% 0/4
90	57.8% 74/128	2.5% 1/40	64.4% 47/73	7.1% 2/28	64.3% 9/14	0% 0/4
120	32.8% 42/128	2.5% 1/40	35.6% 26/73	0% 0/28	28.6% 4/14	0% 0/4

The response rate with BOTOX® tended to be higher for females than for males.

Responder Rates of Glabellar Line Severity
BY SEX

	Investigator's Assessment At Maximum Frown % rated 0 or 1 MALE		Investigator's Assessment At Maximum Frown % rated 0 or 1 FEMALE	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
7	36.6% 15/41	16.7% 2/12	72.7% 117/161	5.1% 3/59
30	53.7% 22/41	8.3% 1/12	82.6% 133/161	4.3% 2/59
60	43.9% 18/41	0% 0/11	71.3% 114/160	3.4% 2/59
90	26.8% 11/41	0% 0/11	50.0% 80/160	5.3% 3/57
120	17/1% 7/41	0% 0/11	26.3% 42/160	3.5% 2/57

Responder Rates of Glabellar Line Severity
BY SEX

	Subject's Assessment % +2 or better MALE		Subject's Assessment % +2 or better FEMALE	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
7	65.9% 27/41	25.0% 3/12	82.6% 133/161	10.2% 6/59
30	70.7% 29/41	16.7% 2/12	93.2% 150/161	10.2% 6/59
60	70.7% 29/41	0% 0/11	81.3% 130/160	6.8% 4/59
90	39.0% 16/41	9.1% 1/11	65.6% 105/160	3.5% 2/57
120	14.6% 6/41	0% 0/11	38.8% 62/160	1.8% 1/57

Results for the two co-primary efficacy variables were similar for Caucasians and non-Caucasians.

Responder Rates of Glabellar Line Severity
BY RACE

	Investigator's Assessment At Maximum Frown % rated 0 or 1 CAUCASIAN		Investigator's Assessment At Maximum Frown % rated 0 or 1 NON-CAUCASIAN	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	76.6% 128/167 –	1.7% 1/60	77.1% 27/35	18.2% 2/11

Responder Rates of Glabellar Line Severity
BY RACE

	Subject's Assessment % +2 or better CAUCASIAN		Subject's Assessment % +2 or better NON-CAUCASIAN	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	88.6% 148/167	11.7% 7/60	88.6% 31/35	9.1% 1/11

Results for the two co-primary efficacy variables were similar regardless of previous BOTOX® treatment.

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Investigator's Assessment At Maximum Frown % rated 0 or 1 YES		Investigator's Assessment At Maximum Frown % rated 0 or 1 NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	86.7% 26/30	0% 0/10	75.0% 129/172	4.9% 3/61

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Subject's Assessment % +2 or better YES		Subject's Assessment % +2 or better NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	93.3% 28/30	10.0% 1/10	87.8% 151/172	11.5% 7/61

The response rate was higher in the BOTOX® treatment group for subjects whose baseline severity score was moderate than for subjects whose baseline severity score was severe.

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE		Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
7	79.5% 66/83	6.9% 2/29	55.5% 66/119	4.9% 2/41
30	92.8% 77/83	3.4% 1/29	65.5% 78/119	2.4% 1/41
60	85.4% 70/82	3.4% 1/29	52.1% 62/119	2.4% 1/41
90	67.1% 55/82	3.6% 1/28	30.3% 36/119	5.0% 2/40
120	37.8% 31/82	3.6% 1/28	15.1% 18/119	2.5% 1/40

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Subject's Assessment % +2 or better MODERATE		Subject's Assessment % +2 or better SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
7	81.9% 68/83	13.8% 4/29	77.3% 92/119	9.8% 4/41
30	90.4% 75/83	13.8% 4/29	87.4% 104/119	7.3% 3/41
60	82.9% 68/82	6.9% 2/29	76.5% 91/119	4.9% 2/41
90	67.1% 55/82	3.6% 1/28	55.5% 66/119	5.0% 2/40
120	42.7% 35/82	0% 0/28	27.7% 33/119	2.5% 1/40

Results for investigator's assessment at maximum frown were statistically significant in favor of the BOTOX® treatment group for:

- Day 7- 8 centers

- Day 30- 9 centers
- Day 60- 7 centers
- Day 90- 3 centers

Results for subject's global assessment were statistically significant in favor of the BOTOX® treatment group for:

- Day 7- 7 centers
- Day 30- 10 centers
- Day 60- 10 centers
- Day 90- 4 centers

Summary of those subjects reporting global assessment of worsening of glabellar line severity

DAY	SCORE	BOTOX® N=202	PLACEBO N=71
7	-1	1 (0.5%)	2 (2.8%)
	-2	0	1 (1.4%)
30	-1	0	4 (5.6%)
60	-1	3 (1.5%)	2 (2.9%)
	-2	1 (0.5%)	0
90	-1	2 (1.0%)	1 (1.5%)
	-2	1 (0.5%)	0
120	-1	5 (2.5%)	2 (2.9%)
	-2	1 (0.5%)	0

Safety:
The safety data included all randomized and treated subjects. There were 202 subjects in the BOTOX® treated group and 70 subjects in the placebo treated group.

No subject died during the study.

No subject discontinued the study because of an adverse event.

There were 4 subjects who reported serious adverse events, 3 in the BOTOX® treated group and 1 in the placebo treated group.

- Subject [redacted] male in the BOTOX® treated group had an elevated alkaline phosphatase level at the Day 120 visit. He had reported a sudden weight loss at Day 90. This subject was later diagnosed with colon cancer (death has been reported 8 months after receiving BOTOX® treatment and 4 months after exit from study).
- Subject [redacted] female who reported back pain approximately 3 months after BOTOX® treatment and was diagnosed with a herniated disc and underwent spinal fusion. She completed the Day 120 follow up

- Subject [redacted] female who began taking Monopril for hypertension approximately 3 months after BOTOX® treatment. The next day she complained of dyspnea and chest pains. She was admitted to the hospital and had a negative work-up. Final diagnosis was anxiety/depression and obesity. The subject completed the Day 120 follow up.
- Subject [redacted] female who received placebo treatment. Three months later, subject underwent a routine colonoscopy and had perforation of the large intestine, which involved hospitalization and surgical correction. The subject completed the Day 120 follow up.

Adverse events were reported for 81 (40.1%) of the BOTOX® treated subjects and 32 (45.7%) of the placebo treated subjects. The most frequently reported adverse event as well as treatment-related adverse event was headache in both groups.

Adverse events reported for ≥ 3% of subjects treated with BOTOX®:

	BOTOX N=202	**PLACEBO** N=70
Any event	81 (40.1%)	32 (45.7%)
Headache	23 (11.4%)	14 (20.0%)
Erythema	6 (3.0%)	2 (2.9%)

There were no significant differences between the treatment groups in the incidence of adverse events. The only difference that approached statistical significance was for edema at the injection site, which was reported in 1 (0.5%) of subjects in the BOTOX® treatment group and 3 (4.3%) of subjects in the placebo group (p= 0.054).

Other adverse events of special interest:

	BOTOX N=202	**PLACEBO** N=70
Burning at injection site	1- Mild 1- Moderate	None
Ecchymosis	1- Mild 1- Moderate	1- Mild 1- Moderate
Erythema at injection site	5- Mild 1- Moderate	2- Mild
Muscle weakness	2- Mild	None
Pain in face	3- Mild 1- Moderate	1- Mild

Pain at injection site	3- Mild 1- Moderate	1- mild
Pruritus	1- Mild	None
Stinging at injection site	2- Mild	None
Twitching	1- Mild 1- Moderate	None
Seeing spots	None	1- Mild

There were two reported cases of blepharoptosis, both treated with BOTOX®

- Subject 3159-Y04 had unilateral ptosis which lasted 52 days
- Subject 3161-159 had bilateral ptosis which was still ongoing at the end of the study by subject's report but not by investigator's assessment

Subgroup analyses of adverse events by age, sex, race and prior BOTOX® treatment showed no statistically significant differences between the treatment groups.

- Overall, there were less adverse events reported in subjects ≤ 50 years of age than ≥ 51 years who were in the BOTOX® treated group (38.3% vs. 43.2%).
- Overall, there were more adverse events reported in subjects ≤ 50 years of age than ≥ 51 years who were in the placebo treated group (52.4% vs. 35.7%).
- Those subjects ≥ 51 years reported less headaches in both treatment groups. No subject ≥ 65 years reported a headache.
- There were more females than males reporting adverse events in the placebo group
- Both treatment groups had a higher proportion of females reporting headaches
- Ptosis was only reported by females (1 ≥ 65 years)
- Ptosis was only reported by Caucasians
- Overall, adverse events were reported for a higher proportion of Caucasian subjects than non-Caucasian in the placebo group.
- Adverse events were reported by a lower proportion of subjects with a history of previous BOTOX® treatment in both groups (33.3% vs. 41.3% for the BOTOX® treated group and 30.0% vs. 48.3% for the placebo treated group).
- Headache was reported for a lower proportion of subjects with a previous history of BOTOX® treatment

Laboratory: Overall individual abnormalities in laboratory variables did not show any clinically meaningful differences between the treatment groups. Triglyceride and glucose values were often reported for many subjects in both groups to be abnormal. For ALT, AST, glucose and triglycerides, more subjects shifted from normal to high after BOTOX® treatment than from normal to low. However, the proportions who shifted were similar between treatment groups except for

glucose, in which 8.7% (17/196) subjects shifted from normal at baseline to high after treatment compared with only 2.9% (2/68) of placebo subjects. Subjects were not fasting for blood draws and the difference was not statistically significant.

- Subject 1938-X02 had an elevated alkaline phosphatase and SGOT which resolved
- Subject 1938-X07 had an elevated alkaline phosphatase which resolved
- Subject 1938-X08 had an elevated SGOT but was lost to follow-up
- Subject 3155-208 had elevated liver enzymes which resolved

There was no statistically significant difference between the groups in changes from baseline to study exit for blood pressure. There was a statistical difference within and between groups in the mean change from baseline in heart rate to study exit but was not clinically relevant. The mean change from Day 0 to study exit were an increase of 2.09 beats per minute for the BOTOX® treatment group and a decrease of 0.80 beats per minute for the placebo group.

There were 190 subjects who had sufficient volume to permit antibody analysis at both pretreatment and posttreatment timepoints.

- 169 subjects were negative at both timepoints for both treatment groups
- 40 matched samples (10.5%) in 20 subjects were inconclusive at 1 or both timepoints.
- 4 matched samples (1.0%) in 2 subjects were positive at 1 of the timepoints
- One subject with matched pretreated and posttreatment serum antibody samples assayed had positive posttreatment samples. This subject was in the placebo treated group.

There were 138 eligible subjects in the BOTOX® treatment group who had sufficient volume to permit antibody analysis at both pretreatment and posttreatment timepoints.

- 126 had negative antibody at both timepoints
- 12 had inconclusive results at 1 or both timepoints
    - 1 had a history of previous BOTOX® treatment
    - 2 subjects with inconclusive pretreatment results responded to BOTOX® treatment
    - Of 8 subjects with negative pretreatment results but inconclusive posttreatment results, 2 (2172-862 and 3161-109) failed to show a response to BOTOX® treatment
    - 1 subject (1901-958) with positive pretreatment results followed by inconclusive posttreatment results responded to BOTOX® treatment
    - 1 subject (3158-U59) with inconclusive results at both timepoints responded to BOTOX® treatment

There were 52 eligible subjects in the placebo treatment group who had sufficient volume to permit antibody analysis at both pretreatment and posttreatment timepoints.

- 43 had a negative result at both timepoints
- 8 had inconclusive results at 1 or both timepoints
    - 2 (3164-357 and 2172-861) had a previous history of BOTOX® treatment
    - 2 subjects with inconclusive results pretreatment and negative results posttreatment did not respond to placebo treatment
    - 6 subjects with negative pretreatment results and inconclusive posttreatment results did not respond to placebo treatment
    - 1 subject with negative pretreatment results and positive posttreatment results had no prior history of BOTOX® treatment and did not respond to placebo

Pooled results of both Phase 3 studies:

These studies were conducted at 29 sites in the US and 1 site in Canada. There were a total of 537 subjects. In both studies, a total of 405 subjects were randomized to BOTOX® treatment and 132 subjects to placebo. Two subjects who were randomized to placebo but never treated were included in the intent-to-treat efficacy analyses.

99.0% (401/405) of the subjects treated with BOTOX completed the 120 day follow-up.

97.0% (128/132) of the subjects treated with placebo completed the 120 day follow-up.

Prior treatment of facial lines with BOTOX® was reported in 14% (75/536) of the enrolled subjects [14.3% (58/405) of the subjects who received BOTOX® and 13.0% (17/131) of the subjects that received placebo]. There was an average of 17.6 months from the first ever, prior treatment with BOTOX® to study entry and there was an average of 9.1 months from the most recent treatment with BOTOX® to study entry.

The Day 0 mean baseline severity score of glabellar line severity at maximum frown based on the investigator's assessment was 2.6 for both groups in both studies (2=moderate and 3=severe).

There were 210 subjects (161 subjects in the BOTOX® treated group and 49 subjects in the placebo treated group) who had glabellar line severity scores at rest of moderate or severe.

The mean age was 46.0 years, from 22 to 78 years. 68.2% (366/537) were ≤ 50 years of age and 31.8% (171/537) were ≥ 51 years of age. 6.0% were ≥ 65 years of age.

Most of the subjects were female, 81.9% (440/537) and Caucasian, 83.8% (450/537).

Pooled Efficacy:
For the primary efficacy variables, the same analysis was applied to the responder score for both variables for the pooled double-blind study data. The analyses were identical to the primary analysis in each study report. For all efficacy analyses of the pooled data, between-group tests were based on the 2-sided null hypothesis that there was no treatment effect versus the alternative hypothesis that there was a treatment effect. The hypothesis test was considered statistically significant if $p \leq 0.05$. Number and percent of responders were calculated and a Mantel-Haenszel test stratified by age group was performed to evaluate the equality of the proportions of responders between groups. Relative risk estimates were calculated using the natural logarithms of the stratum relative risk ratios and precision based weights. The simple difference in the proportions of responders between treatment groups was also estimated and 95% confidence intervals were calculated based on a normal approximation.

Any missing value in the pooled analysis was replaced by the same imputed value used in the individual study analysis. Missing values were replaced only for visits up to and including the Day 30 visit or the exit visit, whichever occurred later.

By Day 7, 75% (299/405) of subjects had achieved a severity score of none or mild at maximum frown by the investigator's assessment. This increased to 80% (325/405) by the efficacy endpoint day of Day 30. Resting appearance as judged by the investigator had 70% (110/161) of subjects achieving a severity score of none or mild at Day 7, and 75% (119/161) by the efficacy endpoint day of Day 30. 80% (334/405) of subjects assessed moderate or better improvement in appearance by Day 7. This increased to 90% (362/405) by the efficacy endpoint day of Day 30.

The responder rates for both co-primary efficacy variables were higher for subjects ≤ 50 years of age than for those ≥ 51 years of age. Efficacy was higher for both groups compared to those subjects ≥ 65 years of age. There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of BOTOX® for the subject's global assessment at all time points except Day 120 ($p \leq 0.036$).

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT MAXIMUM FROWN (% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	73.8% 299/405	6.1% 8/132	67.8% (61.9, 73.7)	<0.001

30	80.2% 325/405	3.0% 4/132	77.2% (72.4, 82.1)	<0.001
60	70.2% 283/403	1.5% 2/130	68.7% (63.7, 73.6)	<0.001
90	47.6% 192/403	2.3% 3/128	45.3% (39.8, 50.8)	<0.001
120	25.3% 102/403	1.6% 2/128	23.8% (19.0, 28.5)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR SUBJECT'S ASSESSMENT OF APPEARANCE
(% and number of subjects with at least moderate improvement)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	82.5% 334/405	9.1% 12/132	73.4% (67.2, 79.5)	<0.001
30	89.4% 362/405	6.8% 9/132	82.6% (77.3, 87.8)	<0.001
60	81.9% 330/403	3.8% 5/130	78.0% (73.0, 83.1)	<0.001
90	63.0% 254/403	3.1% 4/128	59.9% (54.3, 65.5)	<0.001
120	39.0% 157/403	0.8% 1/128	38.2% (33.2, 43.2)	<0.001

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT REST IN SUBJECTS WITH MODERATE OR SEVERE SCORE AT BASELINE
(% and number of subjects with severity of None or Mild)

DAY	BOTOX	PLACEBO	DIFFERENCE	P-VALUE
7	68.3% 110/161	24.5% 12/49	43.8% (29.8, 57.9)	<0.001
30	73.9% 119/161	20.4% 10/49	53.5% (40.3, 66.7)	<0.001
60	72.7% 117/161	24.5% 12/49	48.2% (34.3, 62.1)	<0.001
90	70.8% 114/161	34.7% 17/49	36.1% (21.1, 51.2)	<0.001
120	59.0% 95/161	34.7% 17/49	24.3% (9.0, 39.7)	0.007

95% confidence intervals are shown in parentheses

Responder Rates of Glabellar Line Severity Age
BY AGE DISTRIBUTION

	Investigator's Assessment at Maximum Frown % rated 0 or 1 ≤ 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	80.7% 226/280	5.8% 5/86	58.4% 73/125	6.5% 3/46	34.8% 8/23	11.1% 1/9
30	84.6% 237/280	2.3% 2/86	70.4% 88/125	4/3% 2/46	39.1% 9/23	22.2% 2/9
60	73.6% 206/280	1.2% 1/85	62.6% 77/123	2.2% 1/45	30.4% 7/23	12.5% 1/8
90	50.4% 141/280	1.2% 1/83	41.5% 51/123	4.4% 2/45	30.4% 7/23	12.5% 1/8
120	28.6% 80/280	0% 0/83	17.9% 22/123	4.4% 2/45	4.3% 1/23	12.5% 1/8

Responder Rates of Glabellar Line Severity Age
BY AGE DISTRIBUTION

	Subject's Assessment % +2 or better ≤ 50 years		Subject's Assessment % +2 or better > 50 years		Subject's Assessment % +2 or better > 65 years	
DAY	BOTOX®	Placebo	BOTOX®	Placebo	BOTOX®	Placebo
7	86.8% 243/280	7.0% 6/86	72.8% 91/125	13.0% 6/46	52.2% 12/23	11.1% 1/9
30	91.8% 257/280	3/5% 3/86	84.0% 105/125	13.0% 6/46	69.6% 16/23	11.1% 1/9
60	84.6% 237/280	3.5% 3/85	75.6% 93/123	4.4% 2/45	65.2% 15/23	0% 0/8
90	63.2% 177/280	2.4% 2/83	62.6% 77/123	4.4% 2/45	65.2% 15/23	0% 0/8
120	41.1% 115/280	1.2% 1/83	34.1% 42/123	0% 0/45	17.4% 4.23	0% 0/8

RESPONDER RATES FOR INVESTIGATOR'S ASSESSMENT AT MAXIMUM FROWN (% and number of subjects with severity of None or Mild)
AGE > 65 YEARS

DAY	BOTOX N=23	PLACEBO N=9	DIFFERENCE Botox - Placebo	RELATIVE RISK	P-VALUE
7	34.8% 8/23	11/1% 1/9	23.67 (-4.62, 51.96)	3.13 (0.45, 21.58)	0.188
30	39.1% 9/23	22.2% 2/9	16.91 (-16.8, 50.61)	1.76 (0.47, 6.62)	0.373
60	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85)	0.326
90	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85	0.326
120	4.3% 1/23	12.5% 1/8	-8.15% (-32.5, 16.23)	0.35 (0.02, 4.94)	0.426

95% confidence intervals are shown in parentheses

RESPONDER RATES FOR SUBJECT'S ASSESSMENT OF APPEARANCE (% and number of subjects with at least moderate improvement)
AGE > 65

DAY	BOTOX N=23	PLACEBO N=9	DIFFERENCE	RELATIVE RISK	P-VALUE
7	52.2% 12/23	11/1% 1/9	41.06 (12.11, 70.02)	4.70 (0.71, 31.05)	0.036
30	69.6% 16/23	11/1% 1/9	58.45 (30.61, 86.30)	6.26 (0.97, 40.52)	0.003
60	65.2% 15/23	0.0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
90	65.2% 15/23	0.0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
120	17.4% 4/23	0.0% 0/8	17.39 (1.90, 32.88)	3.38 (0.20, 56.59)	0.214

95% confidence intervals are shown in parentheses

The responder rates for both co-primary efficacy variables were higher for female subjects than for males.

Responder Rates of Glabellar Line Severity
BY SEX

	Investigator's Assessment At Maximum Frown % rated 0 or 1 FEMALE		Investigator's Assessment At Maximum Frown % rated 0 or 1 MALE	
DAY	BOTOX®		BOTOX®	
30	84.7% 283/334		59.2% 42/71	
120	27.7% 92/332		14.1% 10/71	

Responder Rates of Glabellar Line Severity
BY SEX

	Subject's Assessment % +2 or better FEMALE		Subject's Assessment % +2 or better MALE	
DAY	BOTOX®		BOTOX®	
30	93.1% 311/334		71.8% 51/71	
120	42.8% 142/332		21.1% 15/71	

The responder rates for both co-primary efficacy variables were slightly higher for Caucasian than for non-Caucasian subjects.

Responder Rates of Glabellar Line Severity
BY RACE

	Investigator's Assessment At Maximum Frown % rated 0 or 1 CAUCASIAN		Investigator's Assessment At Maximum Frown % rated 0 or 1 NON-CAUCASIAN	
DAY	BOTOX®		BOTOX®	
30	81.2% 277/341		75.0% 48/64	
120	25.7% 87/339		23.4% 15/64	

Responder Rates of Glabellar Line Severity
BY RACE

	Subject's Assessment % +2 or better CAUCASIAN		Subject's Assessment % +2 or better NON-CAUCASIAN	
DAY	BOTOX®		BOTOX®	
30	89.7% 306/341		87.5% 56/64	
120	40.1% 136/339		32.8% 21/64	

Of those subjects in the subgroup who had baseline glabellar line severity scores at rest of moderate to severe, responder rates for both co-primary efficacy variables tended to be higher for subjects with a moderate baseline score than a severe baseline score. The proportion who had their score rated as none to mild at rest after treatment was substantially higher in the BOTOX® treated group as compared to the placebo treated group ($p \leq 0.022$) for every time-point beginning at Day 7 through Day 120 in study 010 and through Day 90 in study 023.

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE		Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	95.8% 159/166	1.8% 1/55	69.5% 166/239	1.4% 1/74
120	39.6% 65/164	1.8% 1/55	15.5% 37/238	1.4% 1/73

Responder Rates of Glabellar Line Severity
BY GLABELLAR LINE SEVERITY

	Subject's Assessment % +2 or better MODERATE		Subject's Assessment % +2 or better SEVERE	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	94.0% 156/166	7.1% 4/56	86.2% 206/239	4.1% 3/74
120	50.6% 83/164	0% 0/55	31.0% 74/239	1.4% 1/73

Most subjects (86.0%, 461/536) had no history of previous BOTOX® treatment for facial lines while 14.0% (75/536) had a previous history of treatment. The response rates for both co-primary efficacy variables tended to be slightly higher for subjects with a BOTOX® treatment history.

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Investigator's Assessment At Maximum Frown % rated 0 or 1 YES		Investigator's Assessment At Maximum Frown % rated 0 or 1 NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	89.7% 52/58	0% 0/17	78.7% 273/347	2.6% 3/114
120	21.4% 12/56	0% 0/17	25.9% 90/347	1.8% 2/111

Responder Rates of Glabellar Line Severity
BY PREVIOUS BOTOX® TREATMENT

	Subject's Assessment % +2 or better YES		Subject's Assessment % +2 or better NO	
DAY	BOTOX®	Placebo	BOTOX®	Placebo
30	91.4% 53/58	5.9% 1/17	89.0% 309/347	6.1% 7/114
120	32.1% 18/56	0% 0/17	40.1% 139/347	0.9% 1/111

The duration of action of BOTOX® for glabellar lines was similar as that noted for other indications, approximately 3-4 months. However, by three months (90 days), almost 50% of subjects still had a severity score of none or mild at maximum frown as assessed by the investigator and 25% showed such a response at Day 120. Treatment effect at rest was still present in 70% (114/161) of subjects at day 90 and 60% (95/161) of subjects at Day 120. Subject's assessment of treatment response was still present in 60% (95/403) of subjects at Day 90 and 40% of subjects at Day 120.

Responder Rates of Glabellar Line Severity

	Investigator's Assessment at Maximum Frown % rated 0 or 1		Subject's Assessment % +2 or better		Investigator's Assessment at Rest % rated 0 or 1	
DAY	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**	**BOTOX®**	**Placebo**
7	73.8% 299/405	6.1% 8/132	82.5% 334/405	9.1% 12/132	68.3% 110/161	24.5% 12/49
30	80.2% 325/405	3.0% 4/132	89.4% 362/404	6.8% 9/132	73.9% 119/161	20.4% 10/49
60	70.2% 283/403	1.5% 2/130	81.9% 330/403	3.8% 5/130	72.7% 117/161	24.5% 12/49
90	47.6% 192/403	2.3% 3/128	63.0% 254/403	3.1% 4/128	70.8% 114/161	34.7% 17/49
120	25.3% 102/403	1.6% 2/128	39.0% 157/403	0.8% 1/128	59.0% 95/161	34.7% 17/49

Responder Rate Difference (BOTOX®- Placebo) For Each Type of Evaluation of Glabellar Line Severity

DAY	Investigator's Assessment at Maximum Frown % rated 0 or 1	Subject's Assessment of Moderate Improvement % +2 or better	Investigator's Assessment at Rest % rated 0 or 1
7	67.8% (61.9, 73.7)	73.4% (67.2, 79.5)	43.8% (29.8, 57.9)
30	77.2% (72.4, 82.1)	82.6% (77.3, 87.8)	53.5% (40.3, 66.7)
60	68.7% (63.7, 73.6)	78.0% (73.0, 83.1)	48.2% (34.3, 62.1)
90	45.3% (39.8, 50.8)	59.9% (54.3, 65.5)	36.1% (21.1, 51.2)
120	23.8% (19.0, 28.5)	38.2% (33.2, 43.2)	24.3% (9.0, 39.7)

95% confidence intervals are shown in parentheses

In both studies, few subjects had severity ratings that increased from baseline to follow-up visits.

Sub. #	Treatment	Age	Sex	Race	Dose #	Day	Score
0093-B06	BOTOX®	37	Female	Cau.	3	60	-2
0093-B57	BOTOX®	57	Female	Cau.	3	90	-1
2127-B09	BOTOX®	46	Female	Cau.	1	120	-1
2425-Z04	BOTOX®	34	Female	Cau.	3	120	-3
2425-Z59	BOTOX®	53	Female	Black	1	120	-1
3159-Y04	BOTOX®	45	Female	Cau.	2	60	-1
					3	30	-1
					3	60	-1
3159-Y07	BOTOX®	42	Male	Cau.	1	60	-1
					1	90	-1
					2	90	-1

					3	30	-2
					3	90	-2
3159-Y60	BOTOX®	53	Female	Cau.	2	90	-2
3161-101	BOTOX®	35	Female	Cau.	1	60	-2
3187-802	BOTOX®	41	Male	Cau.	3	120	-2
3159-Y03	Placebo	54	Male	Cau.	2	90	-1
3187-P12	Placebo	44	Male	Cau.	1	120	-1

Safety:
There were no deaths.

No subject discontinued either study due to an adverse event.

Adverse events of any cause were reported for 43.7% of the BOTOX® treated subjects and 41.5% of the placebo treated subjects. The most frequently reported AEs (>3%) were:

	BOTOX N=405	**PLACEBO** N=130
Headache	13.3%	17.7%
Respiratory infection	3.5%	3.8%
Nausea	3.0%	2.3%
Blepharoptosis	3.2%	0%

Treatment related adverse events were reported for 23.5% of subjects who received BOTOX® and 19.2% of subjects who received placebo. Adverse events of special interest:

	BOTOX N=405	**PLACEBO** N=130
Erythema at injection site	1.7% (7)	1.5% (2)
Pain in face	2.2% (9)	0.8% (1)
Pain at injection site	1.5% (6)	0.8% (1)
Skin tightness	1.0% (4)	0%
Edema injection site	1.5% (6)	2.3% (3)
Paresthesia	1.0% (4)	0.8% (1)
Twitching	0.7% (3)	0%
Muscle weakness	1.7% (7)	0%